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THE JOHNS HOPKINS UNIVERSITY

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THE EXPERIMENTAL ACCELERATION OF THE RATE OF TRANSPORT OF OVA THROUGH THE FALLOPIAN TUBE[1]

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Submitted for publication December 7, 1932

FOREWORD

The present experiments have been planned to determine if the time which is required for the passage of the ovum through the tube may be shortened or lengthened by experimental means. Recently a favorable opportunity for such observations has developed through the use of extracts of human urine of pregnancy or of anterior lobe. It has been observed that the injection of such extracts into pregnant rabbits is followed by the extrusion of a second set of ova into the tubes within about ten hours following the injection (Snyder and Wislocki, 1931). A second ovulation has been induced in rabbits at various stages of pregnancy from the third day until term. It is of interest to observe whether there is, under these unusual conditions, any lengthening or shortening of the time required for transport of the second set of ova through the tubes. There is reason to anticipate a possible alteration in the time of transit of the ova, when it is borne in mind that in pregnancy the contractions and size of the tubal muscle fibers as well as the histological appearance of the mucosa are strikingly different from the character of the tube at ovulation, following normal mating. That the ova themselves in these second, induced ovulations are normal is indicated by the fact that they can be fertilized and caused to segment (Wislocki and Snyder, 1931).

While these striking changes in the tube during pregnancy have long been recognized as a constantly recurring phase of the normal reproductive cycle, it has been scarcely possible to evaluate the func-

[1] This research was aided by a grant from the Linton Fund.

tional significance of the alterations. Since numerous observers have found that normally ova require three days for passage through the tubes, it would seem evident that any alteration in the time required for tubal transit, under the present experimental conditions, might contribute towards an understanding of the nature of the physiological and morphological changes occurring in the tubes during early pregnancy.

EXPERIMENTAL RESULTS

Our results can be summarized briefly by stating that we have found that the time required for the transport of the ova through the tube may be shortened by experimental means. Instead of three days, which is the normal period required by the ova to reach the uterus, it is found that under the conditions of the present experiments ova pass through the tube and can be recovered from the uterus within 60 hours after injection of the extract producing the second ovulation.

The experimental findings are presented in table 1.

The present observations are based upon 14 rabbits. Each animal was isolated in a separate cage for several weeks before the experiment was begun.[2]

In a typical experiment, such as in the case of rabbit no. 1, the doe was mated April 7 at 12:30 P.M. About four days later, on April 11, at noon, injection of 2 cc. of extract of human urine of pregnancy was made into an ear vein, in order to produce a second ovulation. Laparotomy 59 hours later on April 13 at 11 P.M. showed that a second ovulation had occurred. In the right ovary there were two sets of corpora lutea. One set consisted of five large, yellowish corpora lutea, which were evidently older than a second set, six in number, which were smaller and more vascular. The tubes were carefully washed with physiological salt solution, but no ova were found in them. On washing the uterus, however, two sets of ova were recovered. There were four blastocysts and six non-segmented ova, thus accounting for all but one of the ova discharged at the two ovulations. The second set of ova had reached the uterus, therefore, in less than 59 hours following injection of the urine extract.

[2] The extracts of human urine of pregnancy and of anterior lobe were supplied by Parke, Davis and Company.

In rabbits nos. 2 and 3, just as in rabbit no. 1 described above, the tubes and uteri were washed 59 hours following injection of the extract which stimulated the second ovulation. No ova were found in the tubes. Since there were two crops of corpora lutea to be seen in the ovaries, there were evidently 2 sets of ova to be accounted for. In rabbit no. 2 the two crops of ova were readily distinguished, since fertilization had occurred at the first ovulation which followed mating. The blastocysts corresponded in number to the crop of older corpora lutea while the normal unsegmented ova equalled the number of more recent corpora lutea. In rabbit no. 3, normal unsegmented ova were found corresponding in number to the crop of corpora lutea of the second or induced ovulation. Failure to find any trace of the ova of the first ovulation suggested absence of fertilization with subsequent disintegration of the ova during the seven-day interval.

Four rabbits, nos. 4, 5, 6 and 7, were examined 58 hours after injection of the extract which stimulated the second ovulation. It is interesting to note that in each animal of this group one or more ova of the second or induced ovulation were fertilized by introduction of spermatic fluid into the vagina from a pipette, according to the method previously described (Wislocki and Snyder, 1931). At 58 hours following injection of the extract, segmentation had reached the stage of a mulberry-like cell mass or morula, so that identification of this crop of ova was not difficult. Thus in rabbit no. 4 no ova were recovered from the tubes, while in the uterus there were blastocysts corresponding to the ovulation which followed mating, as well as a morula corresponding in development with the interval since the second or induced ovulation. In rabbits nos. 5 and 6, not all of the ova of the second ovulation had reached the uterus and a portion of the crop was recovered from the tubes. In no. 5, there were 2 sets of corpora lutea, but no ova of the ovulation which followed mating were found. Probably fertilization had not occurred and disintegration of the ova followed during the 7-day interval. In no. 6, a set of blastocysts clearly belonged to the first ovulation. The unsegmented ovum and morula which were recovered from the uterus could not be distinguished microscopically from similar ova washed from the tube, and taken together they corresponded in number to the second set of corpora lutea. In rabbit no. 7, the findings were in contrast to those

TABLE 1

Experimental acceleration of the rate of passage of ova through the Fallopian tube

RABBIT NUMBER	DATE OF MATING WITH MALE	DATE OF INJECTION WITH EXTRACT CAUSING SECOND OVULATION	AMOUNT OF EXTRACT INJECTED	TIME ELAPSED FROM MATING UNTIL RECOVERY OF THE OVA FROM THE SECOND OR INDUCED OVULATION	TIME ELAPSED FROM INJECTION OF EXTRACT UNTIL RECOVERY OF THE OVA	OVARIES	UTERUS	TUBES
				days	*hours*			
1	April 7	April 11	2 cc. urine extract	6½	59	2 sets of corpora lutea	(1) Blastocysts (2) Ova, unsegmented, normal	No ova
2	July 3	July 8	5 cc. anterior lobe extract	7	59	2 sets of corpora lutea	(1) Blastocysts (2) Ova, unsegmented, normal	No ova
3	July 3	July 8	3 cc. anterior lobe extract	7	59	2 sets of corpora lutea	(1) Completely degenerated (2) Ova, unsegmented, normal	No ova
4	Oct. 4	Oct. 8	10 cc. urine extract	6½	58	2 sets of corpora lutea	(1) Blastocysts (2) Morula	No ova
5	Sept. 26	Oct. 1	5 cc. urine extract	7½	58	2 sets of corpora lutea	(1) Completely degenerated (2) Ova, unsegmented	(2) Ova, unsegmented; morula
6	Oct. 14	Oct. 18	5 cc. anterior lobe extract	6½	58	2 sets of corpora lutea	(1) Blastocysts (2) Unsegmented ovum; morula	(2) Ova, unsegmented; morula
7	Oct. 7	Oct. 11	10 cc. urine extract	6½	58	2 sets of corpora lutea	(1) Blastocysts	(2) Ovum unsegmented; morula
8	July 13	July 18	6 cc. anterior lobe extract	7	57	2 sets of corpora lutea	(1) Completely degenerated (2) Ova, unsegmented, normal	No ova
9	April 25	May 2	4 cc. urine extract	9	48	2 sets of corpora lutea	(1) Blastocysts	(2) Ova, unsegmented, normal

10	May 4	May 11	3 cc. urine extract	8	33	2 sets of corpora lutea	(1) Blastocysts	(2) Ova, unsegmented, normal
11	April 25	May 1	4 cc. urine extract	7	33	2 sets of corpora lutea	(1) Blastocysts	(2) Ova, unsegmented, normal
12	June 12	June 16	8 cc. anterior lobe	5	33	2 sets of corpora lutea	(1) Blastocysts	(2) Fertilized ova, 4-cell stage
13	May 11	May 14	10 cc. urine extract	4	33	2 sets of corpora lutea	(1) Ova, degenerated	(2) Ova, unsegmented, normal
14	March 12	April 7	2 cc. urine extract	30	96	2 sets of corpora lutea	(1) 30-day fetuses	(2) No ova

(1) = condition of ova (in uterus and tubes) from first ovulation. (2) = condition of ova from second ovulation.

in the three preceding animals examined 58 hours after injection of extract, since none of the ova of the second ovulation had reached the uterus.

In one animal, no. 8, observed 57 hours after injection, the ova of the second ovulation had all reached the uterus and corresponded in number to the corpora lutea of the more recent ovulation.

The limit to the amount of shortening of the period of transit of ova through the tubes was indicated in the findings on rabbits nos. 9, 10, 11, 12 and 13. In rabbit no. 9, which was examined 48 hours after injection of the extract, as well as in the four remaining animals which were studied after an interval of 33 hours following injection, it was evident that ova of the second ovulation had not reached the uterus, as they were always found in the tube.

DISCUSSION

From the foregoing observations it is evident that ova may reach the uterus within 60 hours following injection of hypophyseal extract or concentrated urine of pregnancy. Naturally the period of injection antedates by a few hours the actual rupture of the ovarian follicles, so that the period elapsing between ovulation and arrival of the ova into the uterus is even somewhat briefer than 60 hours. In contrast to this there is ample evidence from the work of Assheton (1894), Gregory (1930), Pincus (1930), as well as others, that the normal period of transit for the ovum is no less than 72 hours. In one instance only, Gregory recorded the time of passage as of 67 hours' duration. We feel justified, consequently, in interpreting our data as indicating that under the conditions of our experiments the passage of the ova has been accelerated.

There is evidence from our various observations that there is no significant difference in the period of time elapsing between normal mating and ovulation, on the one hand, and between injection of an ovulation-inducing substance and rupture of the follicles on the other.

It appears, therefore, that the tubes of the gravid rabbit, characterized as they are by a specific morphology, accelerate the transit of ova which have been introduced into them by experimental procedure. The underlying cause of this phenomenon is, of course, difficult to determine. The tube is generally conceded to be in a quiescent

phase during gestation. This is indicated for the pig by the observations of Seckinger (1923), for the human by Seckinger and Snyder (1926), and for the rabbit in unpublished work by Snyder. If this be the case, we must presume that relative quiescence of the tubal musculature accelerates the passage of the ovum; whereas the phase of relative activity, which reaches its maximum about the time of ovulation, appears to be less conducive to a rapid delivery of the ova into the uterus. Corner (1928) has shown in two experiments that the passage of the ova is apparently delayed by removal of the corpora lutea 15 to 20 hours after mating. In one animal degenerating blastocysts were found in the tubes seven and one-half days after mating; in the other, four unsegmented ova were washed from the tubes four and one-half days after mating. Corner's observations on the influence of removal of corpora lutea, as well as our experiments in which there is an excess of these bodies, suggest that the corpora lutea may play a decisive rôle in determining the physiological state of the tubes and the length of time required for transit of the ova.

What the respective rôles of muscle and mucosa may be in hastening the passage of the eggs in our experiments, it is impossible at present to determine. It appears, however, that diminished muscular tone or diminished tubal peristalsis may facilitate rapid propulsion of the ova into the uterus. Tubal muscle in a more active state encountered by the ova after normal mating, apparently serves to delay the passage or extrusion of the eggs. The physiological state of the isthmus or proximal tubal segment may be the most important factor regulating the passage and release of the ova into the uterus, for, as Andersen's work (1927) shows very clearly, the ovum in its passage through the tube remains for a far longer period in the isthmus than in any other segment. The recent work of Parker on rabbits (1930) implicates the cilia and peristalsis as the major factors in propelling the ova through the tube. The peristaltic movements, according to him, produce temporary compartments in the mucosa which are responsible for currents and counter-currents, in consequence of which particles are transported up or down the tubes. In view of the observations of Andersen upon the retention of the ova for approximately forty-five hours in the isthmus of the tube, it may well be that the additional factor of contracted muscle acts to retard the passage of the eggs. Cer-

tainly the fact that the eggs remain normally in the relatively short tube for three days calls for an explanation of the factors inhibiting the passage of the ova, rather than the factors leading to their transport.

SUMMARY

1. The transit of the ovum through the Fallopian tube can be accelerated experimentally so that the ovum reaches the uterus at least 12 hours sooner than normally.

2. The tubal journey of ova is shortened in pregnant or pseudopregnant animals in which a second ovulation has been artificially induced by extracts of urine or anterior lobe. Ova of the second or induced ovulation reach the uterus in less than 60 hours following injection of the extract.

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THE OCCURRENCE OF MACROCYTIC ANEMIA IN ASSOCIATION WITH DISORDER OF THE LIVER

Together with a Consideration of the Relation of This Anemia to Pernicious Anemia

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Submitted for publication January 20, 1933

The object of this communication is to call attention to the occasional association of macrocytic anemia with disease of the liver. Our interest in this subject was aroused by the discovery of a moderately severe and definitely macrocytic anemia, as well as true (histamine) achlorhydria in a patient whose clinical picture in no way suggested pernicious anemia and who was subsequently found to be suffering from cirrhosis of the liver; and by another patient, encountered shortly afterwards, in whom signs of spinal cord disease and macrocytic anemia were associated with a clinical picture which in other respects suggested cirrhosis or primary malignancy of the liver. This patient's gastric juice contained free hydrochloric acid. Autopsy revealed nodular cirrhosis of the liver and diffuse degenerative changes in the posterior columns of the spinal cord, but there was no evidence of pernicious anemia.

A cursory examination of the common English textbooks failed to reveal any information concerning the occurrence of macrocytic anemia in cirrhosis of the liver.[1] This fact, together with speculations concerning the relation of hepatic disease to pernicious anemia, which is so effectively treated by the administration of liver, led to the investigations here presented.

[1] The only exception is the article of Kelly and Lyon who, in Osler's Modern Medicine, remark that late in the disease "the blood findings may simulate those of pernicious anemia," although they state that the usual finding in cirrhosis is a secondary anemia.

REVIEW OF LITERATURE

A review of the literature (Table I) has shown that the association of macrocytic (hyperchromic) anemia with cirrhosis of the liver is by no means as unusual as the single report in the English journals (35) would suggest. In many instances, the authors reported these cases as similar to pernicious anemia in blood picture, yet clinically quite different. Only in one of Roth's cases were the usual changes characteristic of pernicious anemia discovered at autopsy.

CASES TRACED THROUGH AUTOPSY RECORDS OF THE JOHNS HOPKINS HOSPITAL

We have been able to find in the files of the Department of Pathology 138 cases of cirrhosis of the liver for which adequate clinical data are available. The discovery of instances of macrocytic anemia among these cases is admittedly a difficult task, for in most instances reliance must be placed on the color index, a notoriously inadequate criterion. There are eight cases in which the color index was 1.15 or higher. Two cases (autopsies 2063 and 7677) were recognized clinically as pernicious anemia and this diagnosis was confirmed at autopsy when cirrhosis of the liver, nodular in one case and indefinite in type in the other, was also found. Two other cases (autopsies 3271 and 3313) were complicated by other disorders and are therefore of no value in this discussion. The remaining four cases are of interest.

One patient (autopsy 11320) with extensive syphilitic cirrhosis of the liver and no clinical or autopsy evidence of pernicious anemia aside from a color index varying between 1.15 and 1.40 and a red cell count of 2.5 million, showed free hydrochloric acid of 8 after histamine. Another patient (autopsy 11475) complained of loose bowels, loss of fifty pounds in weight in two years, and swelling of the legs and scrotum, and was found to have a red but not atrophied tongue, a palpable liver, histamine achlorhydria and red cell count of 3.3 million with a color index 1.08 to 1.19 and Price-Jones curve shifted slightly to the right. At autopsy biliary cirrhosis, atrophy and cirrhosis of the pancreas and fatty bone marrow in the femur, were found. The color index of a third patient (autopsy 12808) was consistently 1.2. Free hydrochloric acid was found on gastric analysis. There was no clinical evidence of pernicious anemia. Autopsy revealed biliary cirrhosis of

TABLE I

Cases of cirrhosis of liver with macrocytic (hyperchromic) anemia

AUTHOR	NUMBER OF CASES	TYPE OF CIRRHOSIS	AVERAGE R B.C. IN MILLIONS	REMARKS
Perrin (1908)	1	Atrophic	3.32	Hemoglobin by Tallquist. Macrocytes, microcytes, anisocytosis and poikilocytosis. Typical Laennec's cirrhosis
Talley (1908)	2	Atrophic	1.16	Anemia resembled P. A. Autopsy showed advanced cirrhosis but no P. A., although bone marrow was not examined. No hemorrhages
Roth (1914)	2	Atrophic	1.62	One case P. A. by autopsy as well as clinically. In other jaundice was marked and hemoglobin may not have been accurate. Insufficient microscopic details of blood smear, and no autopsy
Saragea and Seicaresco (1926)	14	Atrophic	3.65	Blood studies seemed to be carefully made. All the patients had ascites
Avezzu (1927)	3	Atrophic	3.76	Macrocytosis confirmed by hematocrit determinations. Mean corpuscular volumes 115, 109 and 113 c.μ, respectively. Ascites in all. No mention of jaundice. No autopsies
Perelli (1928)	10	Atrophic	4.15	Macrocytosis indicated by cell diameter measurements. All well developed cases of cirrhosis. Four had ascites. No mention of jaundice. No autopsies
Masina (1932)	2	Atrophic	2.80	Definite anisocytosis and macrocytosis. Both confirmed at autopsy
Bittorf (1908)	1	Pigmentary	1.78	Typical pigmentary cirrhosis. Also had Addison's disease and hydrothorax. No clinical resemblance to P. A. Blood entirely like that of P. A.
Fiessinger and Laurent (1914)	1	Pigmentary	3.50	No jaundice. Bronzed diabetes with ascites. Leucopenia. Nucleated red cells. Autopsy—hemochromatosis, perihepatitis, annular cirrhosis, tbc peritonitis, atrophy pancreas and adrenals and tubular nephritis
Levy and Jausion (1925)	1	Pigmentary	3.20	Bronzed diabetes. No ascites. Diarrhoea. Wassermann positive. Symptoms improved on anti-luetic treatment. No autopsy

TABLE I—*Concluded*

AUTHOR	NUMBER OF CASES	TYPE OF CIRRHOSIS	AVERAGE R.B.C. IN MILLIONS	REMARKS
Gamna (1927)	2	Pigmentary	2.58	No jaundice. Achylia and combined sclerosis in one case. Macrocytosis confirmed by diameter measurements. Leucopenia and relative lymphocytosis. No evidence of P. A. at autopsy
Eppinger (1920)	1	Cirrhosis with hemosiderosis	1.30	Jaundice. Ascites. C. I. 1.9. Many megalocytes; polychromatophilia and normoblasts. Fragility of red cells 0.50 to 0.34. Achlorhydria. P. A. considered definitely ruled out at autopsy
Perelli (1928)	2	Syphilitic	2.95	Well marked cases of cirrhosis. Macrocytosis determined by cell-diameter measurements
Türk (1912)	1	Early cirrhosis—Type?	1.86	Described as "Severe, cryptogenic, hemolytic (pernicious-like) anemia with enlarged liver and spleen." At autopsy, bone marrow, spleen and liver not at all suggestive of P. A.
Hayem (1889)	1	Hypertrophic	1.79	Jaundice. Ascites. Blood picture considered very similar to that of P. A., yet autopsy revealed no evidence of the latter
Cabot (1897)	1	Hypertrophic	2.06	Jaundice transient. Leucopenia. No autopsy
Haan (1898)	6	Hypertrophic	3.21	All had jaundice, persistent or intermittent. Only one had ascites. Three had Ewald G-A: all showed free HCl. Only one complicated (mild bronchitis). Two showed leucopenia. One autopsy
Hoke (1889 and 1901)	2	Hypertrophic	1.31	Hemoglobin by von Fleischl method. Blood considered to resemble P. A. Both had subicteric tinge. First showed only trace of free HCl after test meal of liter of milk. Second showed occasional nucleated red cells. No autopsies
Saragea and Secaresco (1926)	4	Hypertrophic	3.74	All had ascites

the liver. The fourth patient (autopsy 3661) was found to have carcinoma of the pancreas with metastases in the liver, a small echinococcus cyst of the liver, as well as biliary cirrhosis. Five blood studies were done on this negro laborer over a period of six weeks. The red cells progressively fell from 4.77 to 3.23 million while the color index varied from 1.0 to 1.36, averaging 1.15. Free hydrochloric acid (47 cc. per cent) was found in the gastric juice.

CASES STUDIED

Among forty-three cases of hepatic disorder as widely varied in etiology as chronic passive congestion, cirrhosis, carcinoma and acute yellow atrophy, we have encountered eleven instances of macrocytosis. In examining the blood of these patients we have used methods, fully described elsewhere (39), which, we believe, serve to indicate accurately the presence and degree of macrocytosis. It is not intended at this time to give a detailed account of the blood examinations in the non-macrocytic cases. It will suffice here to say that, of the thirty-two instances in which macrocytosis was not observed, anemia of even slight degree was present in only seventeen cases. In eleven of the latter the anemia was associated with no significant change in the mean volume or hemoglobin content of the erythrocytes. In four cases there was slight microcytosis and in the two remaining cases the anemia was of the hypochromic microcytic type. In both of the latter cases hemorrhage had occurred and probably accounted for the type of anemia encountered.

The pertinent data concerning the eleven instances of macrocytosis are summarized in Table II. The histories of several of these cases, however, merit presentation in somewhat greater detail.

Nodular cirrhosis of liver with extreme jaundice, splenomegaly, persistent macrocytic anemia not responding to liver or ventriculin therapy, marked degenerative changes in spinal cord, hydrochloric acid found in stomach only on histamine stimulation

A. Z. (J.H.H., U. 32868, Autopsy 12105), white male, 50 years, Italian, appeared at the J. H. H. January 1930 for the first time on account of pain in the stomach, weakness, nausea, occasional vomiting, loss of weight and constipation. In addition to emaciation, pallor of the mucous membranes and a tinge of jaundice, an enlarged liver (4 f.b. below costal margin) and large bilateral inguinal herniae were found. Erythrocytes numbered 3.24 million, the hemoglobin was 64 per cent, color index 1.0. The Wassermann was negative, the Van den Bergh

TABLE II

Cases of macrocytosis associated with liver disorder

PATIENT	CLINICAL DIAGNOSIS	GASTRIC ANALYSIS FREE HCl	SIGNS OF SPINAL CORD DEGENERATION	OTHER SYMPTOMS OF PERNICIOUS ANEMIA	COURSE	BLOOD						ICTERUS INDEX	SUBSEQUENT CHANGES IN BLOOD
						R.B.C.	Hb	R.B.C.	C.V.*	C.H.	C.C.		
						millions	*gm. per 100 cc.*	*vol. cc. per 100 cc.*	*c. μ*	*γ γ*	*per cent*		
C. C. U 33698	Cirrhosis of liver	0 (histamine)	None	None	Diagnosis confirmed at operation (omentopexy). Death following hematemesis	3.14	13.0	35.3	112	41	37	50	No change in 10 days
A. Z. U 32868	Cirrhosis of liver; combined sclerosis	0 (Ewald) 48 (histamine)	Present	Pap. atrophy at margin of tongue	Autopsy: nodular cirrhosis of liver. Splenomegaly. Diffuse degeneration in spinal cord. Moderate hyperplasia in bone marrow	3.64	13.3	37.0	102	37	36	45	Spontaneous (?) improvement
P. M. U 42899	Hepatomegaly; biliary cirrhosis of liver (?)	30 (histamine)	None	None	Little change in 8 months	4.20	13.1	42.8	102	31	31	18	Slight increase of anemia
M. M. U 43330	Psoriasis; hepatomegaly—unexplained	28 (fasting) 38 (histamine)	N. and T. in legs. Vib. sense decreased	None	Psoriasis greatly improved. Hepatomegaly and nervous symptoms persist	3.66	12.7	41.5	114	35	31	7.5	After 33 days R.B.C. rose spontaneously to 4.67, C.V. dropped to 101
R. J. U 43368	Infectious arthritis; hepatomegaly—unexplained	Not done	None	None	Arthritis and general condition greatly improved but hepatomegaly persists	2.45	7.7	26.0	106	31	30	7.5	Spontaneous improvement
U. L. U 42742	Hepatomegaly—carcinoma (primary in stomach?)	45 (histamine)	None	None	Death—no autopsy	2.96	11.2	32.6	110	38	30	10	Spontaneous improvement in 12 days

J. H. U 45709	Carcinoma of liver; cirrhosis of liver	67 (histamine)	None	None	Autopsy: moderate cirrhosis of liver; primary liver cell carcinoma with metastases to remainder of liver	3.15	11.8	31.7	101	37	37	35	Retic. response to intram. liver
W.B. U 45999	Carcinoma, head of pancreas	0 (histamine)	None	None	Death following exploratory. Autopsy: Carcinoma tail of pancreas, metastases to liver, lymph nodes, vertebra, gall-bladder, peritoneum. Ascites. Arteriosclerosis	5.04	14.9	49.2	98	30	30	35	No change in 4 days
C. S. U 34300	Arteriosclerosis; bronchiectasis; amyloidosis; uremia; prostatic hypertrophy	0 (histamine)	None	None	Autopsy: emphysema, *bronchiectasis*. *Amyloidosis* of liver, spleen, thyroid and kidneys. Cavernous hemanginoma of liver. Hyperplastic femoral bone marrow	2.48	8.5	26.2	106	34	33	3	Spontaneous improvement in 18 days
A. H. U 42098	Acute catarrhal jaundice	0 (histamine) followed by 10 (histamine) 26 days later and 36 (Ewald) 101 days later	None	None	Spontaneous recovery	3.20	11.0	30.7	96	34	30	80	Spontaneous improvement in 24 days
V. V. U 44041	Arteriosclerosis, hypertension; myocardial insufficiency; chronic passive congestion of liver	0 (histamine)	None	None	Improved. Liver returned to normal size	4.28	14.4	42.8	100	34	34	7.5	In 10 days R. B. C. 4.71 C.V. 99

* C.V. refers to mean corpuscular volume and is expressed in cubic microns; C.H. refers to mean corpuscular hemoglobin which is expressed in micromicrograms, and C.C. is mean corpuscular hemoglobin concentration, expressed in per cent.

4.4 mgm., biphasic. No free hydrochloric acid was found in the gastric contents following an Ewald meal, but after histamine stimulation there were 48 cc. of N/10 hydrochloric acid per 100 cc. of gastric juice.

In August 1930 the gall-bladder showed practically no dye by the visualization test. Bile was present in the urine, the stools were lighter than normal but not clay-colored. The jaundice was deeper. Later in the month the herniae were repaired.

In February 1931, the patient came to the Neurological Dispensary because of pain in the knees and some difficulty in walking. The latter had been present for two years but had become very much worse during the preceding six weeks. There was also loss of libido. The knee and ankle jerks were absent, vibratory sense was absent in the feet, the gait was unsteady. Tabes dorsalis was considered but the blood Wassermann and spinal fluid were negative. On February 28, 1931, the erythrocyte count was 3.64 million, hemoglobin 13.3 grams (92 per cent), and the mean corpuscular volume 102 c.μ[2] (color index 1.5).

On admission to the Medical Service later in the same month, a history of constant though moderate drinking of alcoholic beverages was elicited. The patient had had few illnesses and no infections. The temperature was 99.6°, pulse 84, respirations 16 and B.P. 110/70. He was markedly undernourished and deeply jaundiced. Pallor of the mucous membranes, rather marked papillary atrophy at the lateral margins of the tongue, prominent veins over the abdomen and lower part of the chest, a firm liver with roughened surface extending 4 cm. below the costal margin, absent abdominal, cremasteric, patellar and ankle reflexes, and loss of vibratory sense, muscular wasting in the legs and faltering gait with a wide base, were the findings of interest. There was no ascites, glandular enlargement, or loss of position sense. In the urine, bile pigment and urobilin were found. The stools were dark brown and formed. The Van den Bergh gave a prompt, biphasic reaction, 5.0 mgm. per cent. Roentgen rays of the gastrointestinal tract, long bones and spine were negative.

Repeated blood examinations were made. On March 4, the red cell count was 3.65 million, the hemoglobin 13.4 grams (93 per cent) and the mean corpuscular volume 100 c.μ (color index 1.25). On March 7, the erythrocytes numbered 3.68 million, the mean corpuscular volume was 102 c.μ, the mean corpuscular hemoglobin 36$\gamma\gamma$, and the mean corpuscular hemoglobin concentration 35 per cent. The leukocytes varied from 6,000 to 8,000. The differential count was normal. In the blood smear a few microcytes and many macrocytes were noted (fig. 1), but there was little poikilocytosis. Platelets were slightly reduced in number (170,000). In view of the macrocytosis, therapy with liver extract (Lilly, No. 343), six vials daily, was commenced on March 11, but, after the patient was dis-

[2] The normal range of mean corpuscular volume is 80 to 94 c.μ, of mean corpuscular hemoglobin 28 to 32 $\gamma\gamma$, of mean corpuscular hemoglobin concentration 32 to 36 per cent.

charged, ten days later, liver extract was taken very irregularly. No change in the percentage of reticulocytes followed the institution of liver therapy. Although the anemia was slightly less marked when the patient was next seen on April 21, (R.B.C. 4.34, hemoglobin 13.0 grams, mean corpuscular volume 92 c.μ), it is questionable whether this change was caused by the small amount of liver extract taken.

In July 1931, the red count was 4.21, hemoglobin 14.3 grams and mean corpuscular volume 97 c.μ. Although the anemia was less marked, the illness was steadily advancing. The appetite was very poor, the weakness was greater, and loss of weight more marked. The jaundice was much more intense (icterus index 125). The liver was still quite large and firm. The neurologic symptoms had become much more noticeable and, in addition to the previous symptoms, there were sensations of pins and needles in the hands as well as inability to button the clothes because of numbness.

The patient was readmitted in July 1931. Another attempt was made to influence the anemia by administering desiccated hog stomach (Ventriculin) three vials daily. The patient became progressively more drowsy and weak. The anemia remained unchanged and therapy was terminated after ten days by death. On the day of death the red cell count was 4.16 million, hemoglobin 15.1 grams and mean corpuscular volume 96 c.μ.

Autopsy revealed advanced nodular cirrhosis of the liver and some ascites. There was such extensive scarring of the liver that it was suggested that at one time there may have been acute or subacute yellow atrophy. The spleen was enlarged and in places the sinuses were filled with myeloid elements. There was an abundance of iron but no extensive hematopoiesis. Fat necroses were present in the pancreas. There was moderate hyperplasia in the bone marrow. In the posterior columns of the spinal cord there were diffuse degenerative changes.

Cirrhosis and carcinoma of the liver, high gastric acidity, macrocytic anemia, maximal reticulocyte response to intramuscular liver therapy

J. H. (J.H.H., U. 45709, Autopsy 12917), white male, 65 years, appeared on October 5, 1932, with the complaints of weakness, jaundice and swelling of the abdomen of six months' duration, loss of weight and swelling of the legs in the past three weeks. A gradual tanning of the face and hands had occurred in the past year. In the past four months there had been some epistaxis about once a week but the total amount of blood lost had been only slight. The skin of his face, neck and hands was tanned and the conjunctivae, mucous membranes and body were deeply jaundiced. There was no papillary atrophy of the tongue. The abdomen was prominent and a crown of dilated venules was noted in the right upper quadrant. There was moderate edema of the skin over the abdomen and moderate ascites was made out. A hard, nodular mass which was taken to be liver filled the upper right quadrant and extended to the left mammary line. The spleen was not felt. There was some edema over the sacrum and rather

marked edema of the legs. The knee jerks and ankle jerks could not be elicited but other reflexes were normal and no disturbances in sensation or coordination were made out.

After histamine stimulation 67 cc. of N/10 free hydrochloric acid were found on gastric analysis. X-rays failed to reveal any abdominal tumor other than the mass above mentioned. The Van den Bergh read "delayed, biphasic, 5.0 mgm. per cent." Bile, urobilin and bile salts were found in the urine, as well as a reducing substance which was subsequently shown to be a bile salt. The Rous test for hemosiderin in the urine was positive on one occasion but negative on further tests. The stools showed decreased bile pigment from time to time but were never achylic. Skin biopsy was negative for iron-containing pigment.

On October 8, the erythrocyte count was 3.15 million, the hemoglobin 11.8 grams, the mean corpuscular volume 101 c.μ, the mean corpuscular hemoglobin concentration 37 per cent and the mean cell diameter 8.47μ (normal control 7.5μ). The majority of the red cells in the blood smear appeared large, but there was an occasional exceptionally large cell and a more rare microcyte. There was slight poikilocytosis but no achromia, stippling, polychromatophilia or nucleated red cells. Leucocytes, 4,850. The decrease was at the expense of the lymphocytes.

In view of the macrocytic anemia, liver therapy was attempted. On three successive days liver extract (Lederle, 3 cc.) was injected intramuscularly and on the two succeeding days liver extract (Lilly, 5 cc.). The reticulocytes rose from 0.2 per cent on the first day of injection to a maximum of 10.2 per cent on the seventh day after treatment was instituted (fig. 2). This rise was in excess of the calculated (30) maximum reticulocyte response which would have been expected at this red cell count in pernicious anemia. This reticulocyte response was followed by a rise in the erythrocyte count to 3.82 million and a decrease in macrocytosis, the mean corpuscular volume becoming 92 c.μ twelve days after treatment had been instituted (October 12). Two further injections of liver extract (Lederle 3 cc.) were followed by a rise in reticulocytes to a peak of 3.8 per cent on the fifth day (October 27) following injection.

No further treatment was given. Although the anemia remained unchanged, the patient steadily grew worse; weakness, emaciation, and swelling of the abdomen and legs became greater, the jaundice grew deeper and finally he died on December 20, 1932.

Autopsy revealed primary liver cell carcinoma (right lobe) with metastases to the remainder of the liver, and to the lungs, and peritoneal implants in the rectovesical pouches and capsule of the spleen. The liver weighed 4700 grams. The greater part of the right lobe was occupied by a tumor mass; the left lobe was riddled with metastases which in no situation were more than 3 to 4 cm. apart. On microscopic examination the tumor masses were found to be composed of strands or cords of cells which simulated very closely normal liver cells both in appearance and in structural arrangement. In many places double rows of cells were separated by a fine space in which bile could be distinctly seen and which evidently represented an attempt at the formation of bile canaliculi. The same appearance was found in all the metastases.

Not more than a quarter of the amount of liver tissue normally present was uninvaded by tumor cells. Microscopic examination of such portions revealed considerable distortion of the liver lobules. Their central portions showed marked atrophy of the liver cells but there was little necrosis. The portal areas contained a considerably increased amount of fibrous scar tissue and in some areas sprouting of bile-ducts could be made out.

There was no evidence of extramedullary blood formation in the liver, spleen or kidneys. The spleen showed chronic passive congestion. The femoral bone marrow was fatty; that of the vertebrae, the usual red. The bone marrow of the sternum was deep red and very soft. On microscopic examination the bone marrow was considered normal.

Acute catarrhal jaundice with achlorhydria (histamine) and macrocytic anemia followed by spontaneous recovery and disappearance of anemia as well as return of free hydrochloric acid

A. H. (U. 42098), a woman of 42 years, had been perfectly well until nine days before admission (February 22, 1932). At that time, "yellow spots" appeared on her face and soon anorexia and nausea followed. She vomited three times on the second day of her illness. The stools became light in color and the urine dark. She came to the hospital, March 3, 1932, feeling weak and stuporous and was found to be markedly jaundiced. There was evidence of some recent loss of weight. The liver was greatly enlarged, extending at one point almost to the right anterior iliac spine. The spleen could not be felt. There were no other noteworthy physical findings. The tongue showed no papillary atrophy and there were no neurologic symptoms or signs. The stools were light brown in color, the urine contained large quantities of bile and urobilin, the Van den Bergh test was reported "prompt biphasic, 10 mgm. per cent." Ten days after the onset of the illness, no free hydrochloric acid was found on gastric analysis even after histamine stimulation. The erythrocyte count was 3.20 million, the mean corpuscular volume 96 c.μ.

Although there was at first some debate concerning the diagnosis, the consensus of opinion favored acute catarrhal jaundice and the subsequent course of events was that typical of this disease. The jaundice soon began to clear up and the liver decreased in size. The erythrocyte count gradually rose and the red cells became smaller. Twenty-four days after the above blood findings were recorded (March 28, 1932), the red corpuscles numbered 4.55 million and the mean corpuscular volume was 81 c.μ. Interestingly enough, at this time gastric analysis showed the presence of ten units of free hydrochloric acid. The patient was again seen three months later when she was found to be quite well. There was no evidence of biliary obstruction in her appearance, blood plasma or urine. By gall-bladder visualization and duodenal drainage no abnormalities could be detected. The liver could not be felt. Gastric analysis revealed a free hydrochloric acid of 36.

Study of the blood of the eleven cases with macrocytosis has revealed certain features which were observed with such consistency that they may be briefly described.

1. Although the macrocytosis was quite definite, the *anemia* itself was slight or *moderate* when compared with the gravity of the patients' illness.

The lowest red cell count was 2.42 million and in 8 instances the *lowest* levels of the red cell counts were 2.5 to 3.7 million. In two cases an increased mean corpuscular volume was found even in the absence of anemia (patients W. B. and V. V.) and in another (M. M.) the macrocytosis did not entirely disappear even though the red cell count had risen to normal.

2. In at least 5 out of 8 patients on whom satisfactory observations could be made, *remission* in the severity of the anemia took place although no therapy was employed. These spontaneous remissions occurred with surprising rapidity and were accompanied, as in pernicious anemia (40), by a decrease in the mean corpuscular volume.

The disappearance of anemia and macrocytosis with the subsidence of an attack of acute catarrhal jaundice in patient A. H. has already been described. There was little change in the blood of R. J. during a period of twenty days while he was observed in the hospital, but when he was next seen, 3½ months later, the red cells numbered 4.44 million and the mean corpuscular volume was 91 c.μ. The arthritis had greatly improved. The liver, nevertheless, was as large as ever.

The spontaneous remissions are of special interest because in several cases blood remission took place in the face of clinical aggravation. Thus, in patient U. L. the red cell count rose from 2.96 to 4.08 million and the mean corpuscular volume fell from 110 c.μ to 88 c.μ in 12 days although his general condition was gradually becoming worse. In patient C. S. the count rose spontaneously from 2.48 to 3.45 million and the mean corpuscular volume fell from 106 to 87 c.μ in 18 days. He died several weeks later without any further change in the blood taking place.

3. The macrocytosis seemed to be a characteristic of the great majority of the red cells.

Most of the erythrocytes in the blood smears appeared larger than normal and there was little anisocytosis. In many cases only a few outstanding macrocytes, rare microcytes and little or no poikilocytosis were found. The diameter distribution curves of the red cells of these

cases, however, seem to be like those of cases of pernicious anemia with similarly moderate grades of anemia (see figs. 1 and 3).

Liver therapy was attempted in four cases. Only in one was the administration of liver followed by a definite reticulocyte response.

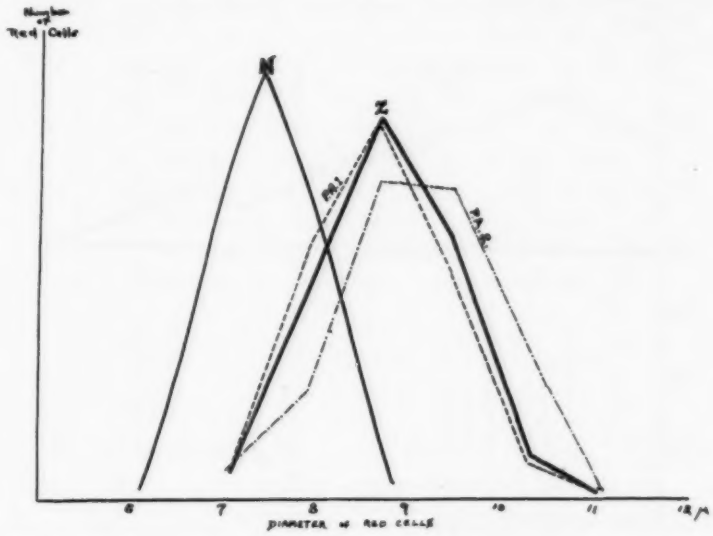

FIG. 1. THE DISTRIBUTION OF RED CELL DIAMETERS IN A CASE OF CIRRHOSIS OF THE LIVER COMPARED WITH THAT OF NORMAL BLOOD AND OF TWO CASES OF PERNICIOUS ANEMIA

— N. Normal distribution of red cell diameter.

— Z. Distribution in patient A. Z. at the time red cells numbered 3.87 and mean corpuscular volume was 91 c.μ.

– – P.A.$_1$. Distribution in a case of pernicious anemia. R.B.C., 3.85 million, mean corpuscular volume 93 c.μ.

—·— P.A.$_2$. Pernicious anemia, R.B.C., 3.11 million, mean corpuscular volume 113 c.μ.

Patient C. S. was given daily for fourteen days Castle's liver extract, 400 grams, at a time when his red cell count was 3.36 million. The reticulocytes remained at 0.6 per cent and the erythrocyte count was likewise not changed. Patient U. L. was given liver extract

(Lederle) intramuscularly, 3 cc. daily on three successive days. The day treatment was instituted the erythrocyte count was 3.72 million. Although a week later the red cells numbered 4.06 million, the hemo-

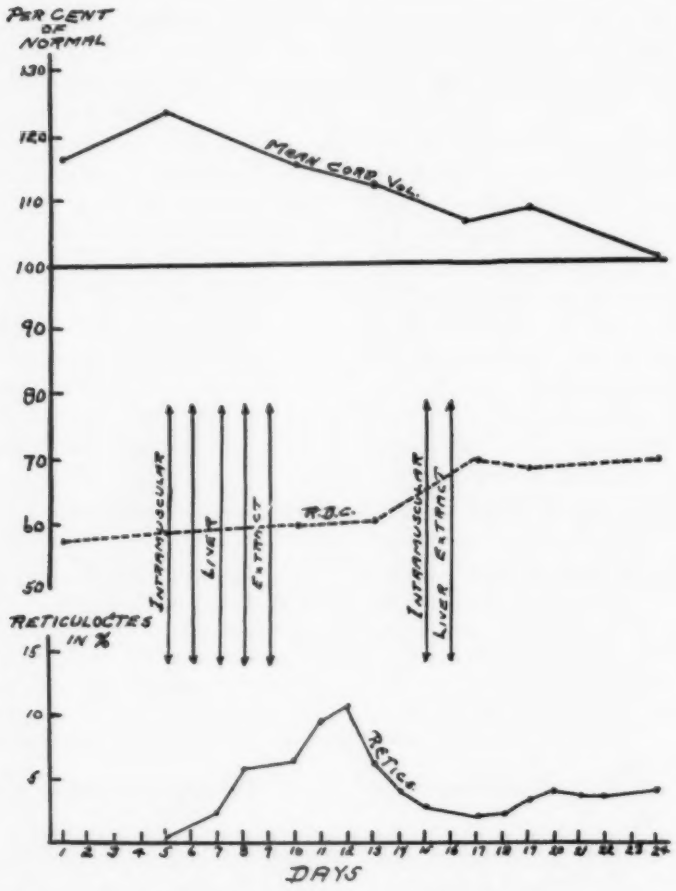

FIG. 2. THE RESPONSE TO INTRAMUSCULAR LIVER THERAPY IN J. H.

The mean corpuscular volume and red cell count are expressed in proportion to the normal values, the ideal for both being 100 per cent.

globin and volume of packed red cells did not increase and the reticulocytes, counted daily, fluctuated between 1.1 and 0.3 per cent without any tendency to rise or fall. Two weeks after treatment the red cell count was 4.10 million and three weeks later it was 4.06.

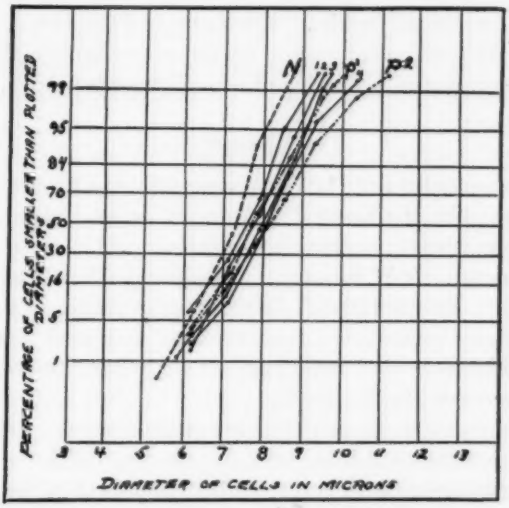

FIG. 3. SUMMATION DIAMETER FREQUENCY CURVES OF RED CELLS FROM CASES OF HEPATIC DISORDER ASSOCIATED WITH MACROCYTOSIS, COMPARED WITH CURVES OF RED CELLS FROM NORMAL AND PERNICIOUS ANEMIA BLOOD (ON ARITHMETIC PROBABILITY PAPER)

Curve N: Normal red cells. Mean diameter 7.51 μ. R.B.C. 5,100,000, Mean Corp. Volume 86 c.μ.

Curve 1: Patient A. Z. (October 5, 1931). Mean diameter 7.98 μ. R.B.C. 3,870,000. Mean Corp. Volume 93 c.μ.

Curve 2: Patient W. B. Mean diameter 8.02 μ. R.B.C. 5,060,000. Mean Corp. Volume 99 c.μ.

Curve 3: Patient A. Z. (February 28, 1931). Mean diameter 8.32 μ. R.B.C. 3,640,000. Mean Corp. Volume 102 c.μ.

Curve 4: Patient J. H. Mean diameter 8.47 μ. R.B.C. 3,150,000. Mean Corp. Volume 101 c.μ.

Curve P^1: Pernicious anemia. Mean diameter 8.17 μ. R.B.C. 3,850,000. Mean Corp. Volume 95 c.μ.

Curve P^2: Pernicious anemia. Mean diameter 8.64 μ. R.B.C. 3,110,000. Mean Corp. Volume 113 c.μ.

It is only fair to point out, however, that in both of the above mentioned patients, what seemed to have been a spontaneous rise in the red cell count had already taken place shortly before liver therapy was attempted. Whether this played any rôle in the failure to respond to liver therapy cannot be decided. In patient A. Z. liver therapy was followed by equivocal results. There can be little doubt, however, concerning the positive influence of the intramuscular injection of liver extract on the blood of J. H. whose history is recorded above.

DISCUSSION

The cases recorded and the cases reported in the literature, as well as those found in the hospital records, indicate without reasonable doubt that macrocytic anemia may be encountered in association with hepatic disorder. It is, however, hardly of any advantage to discuss at this time in any great detail the possible significance of this macrocytosis. Many explanations come to mind and studies are now in progress which may shed some light on this point. Brief consideration may, however, be of interest.

It does not seem likely that the cases under discussion are instances of pernicious anemia which happen to be associated with liver disorder. The strongest presumptive evidence in this respect is the fact that, among the ten cases in which gastric analysis was carried out, free hydrochloric acid was found in six. Unfortunately, it has so far not been possible to test the gastric juice of these patients for the "intrinsic factor" of Castle (7).[3]

An important question which arises is, whether the macrocytosis observed cannot be explained on the basis of alterations in the circulating red cells due to physical-chemical factors. It does not seem that the presence of bilirubin is the cause of such a change, for (1) in five of the cases no jaundice was present; (2) we have observed many instances of jaundice not associated with liver disorder, in which macrocytosis was not present; and (3) in the patient whose blood responded to liver therapy (J. H.), macrocytosis disappeared although the bilirubinemia continued to increase. Whether other chemical constituents

[3] Since submission of this manuscript the presence of intrinsic factor has been demonstrated in the gastric juice of patient P. M. (Table II).

in the blood plasma may have led to swelling of the red cells in these cases is less easily decided.

It is tempting to link the observations here recorded with what is known about pernicious anemia. It has been demonstrated (34, 19, 29) that in the liver is stored a hematopoietic principle which is necessary for normal blood formation. If this be true, it might be expected that extensive damage of the liver would so impair this function that macrocytic anemia might develop. The response to the intramuscular injection of a liver extract potent in pernicious anemia, noted in patient J. H., suggests a close relationship between the macrocytosis encountered in these cases of liver disorder and the macrocytic anemia of pernicious anemia, sprue (40), and some cases of tropical anemia (38) and celiac disease (37). As far as we are aware, reticulocyte response to intramuscular liver therapy is limited to these anemias which, according to recent investigations (34), are very similar in their fundamental nature.

Why macrocytosis is not found in every case of hepatic disorder, and what is the significance of the achlorhydria encountered in some of the cases, are important questions. The course of events in patient A. H. suggests a possible relation between defective gastric secretion, hepatic disorder and macrocytosis. Recent investigations have indicated how important for normal blood formation is the integrity of the gastric function (7, 34). Other observations suggest that variations in the degree of gastric defect are to be encountered, and that the type of gastric derangement found in well developed pernicious anemia represents an end stage (8). It seems quite plausible that a state of gastric deficiency may exist which is not of itself sufficient to produce anemia under the ordinary stresses of life, but, when faulty storage (and elaboration?) of the hematopoietic principle as a result of hepatic disorder is added, the normal hematopoietic process may become adversely affected. It may be that, in some of the observed cases, degrees of gastric defect and of liver damage, alone insufficient to lead to the development of anemia, in combination have been sufficient to do so. In other instances it is possible that the liver damage was so extensive or of such a nature that this alone sufficed to produce anemia. It is of interest, although it may be pure coincidence, that in the eight cases autopsied at this hospital, the pathologist stated that the extent

of liver destruction was extreme in the very same four cases in which hydrochloric acid was found in the gastric contents, whereas in the four cases in which achlorhydria was present there is no such comment.

SUMMARY AND CONCLUSIONS

1. The histories of three patients who showed macrocytic anemia in association with disease of the liver, and data concerning eight other instances of macrocytosis associated with hepatic disorder, are presented. Autopsy was performed in four of these cases and five patients are still living. In none were any of the known causes of macrocytic anemia discovered.

2. Reports of similar cases have been collected and data concerning several additional cases discovered in the hospital records have been added.

3. This macrocytic anemia encountered in association with disease of the liver is described.

(1) It is usually only moderate in degree.

(2) The macrocytosis is rather uniform so that there is little anisocytosis and practically no poikilocytosis.

(3) Rapid spontaneous blood remissions occurred in several of the cases, although in only two cases was the decrease in the severity of the anemia associated with definite clinical improvement.

(4) A clear-cut response to liver therapy was not observed in three cases but in a fourth maximal response of reticulocytes occurred.

4. The cause of the anemia is discussed in regard to

(1) The accidental coexistence of pernicious anemia in these cases;

(2) The rôle of jaundice and other factors in the production of the macrocytosis through physico-chemical influence on the circulating erythrocytes; and

(3) The relation of functional changes in the liver and of achlorhydria to the development of the anemia.

5. It is suggested that in the liver is stored, and possibly further elaborated, the hematopoietic principle produced by the interaction of the intrinsic and extrinsic factors of Castle and that, in addition to macrocytic anemia occurring as a consequence of the absence of the

intrinsic factor in the gastric secretion or the lack of the extrinsic factor in the diet, this type of anemia may occur,

(1) as a result of such liver disturbance as impairs the storage of the hematopoietic principle in the liver; and

(2) by a combination of partial gastric disturbance and incomplete liver damage.

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THE USE OF SUPRARENAL CORTEX IN THE TREATMENT OF DISORDERS OF THE THYROID GLAND

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The etiology of hyperthyroidism is obscure and until recent years its therapy has been in an unsettled state. There are patients who do not respond to the usual non-operative procedures of rest, sedatives, high calorie diets, hydrotherapy, iodine administration, x-ray or radium application, or to the operative procedure of sub-total lobectomy. The failure of these therapeutic measures emphasizes the uncertain cause of the malady.

This report concerns one of the non-operative procedures, namely, the administration of a gland extract, in this instance of the cortical portion of the beef suprarenal gland (1) and the feeding of raw suprarenal cortical tissue to patients suffering from hyperthyroidism.

Solis-Cohen (2), years ago, elaborated on the cause and treatment of exophthalmic goiter. He believed the essential disturbance to be an incoördination or ataxia of the circulatory mechanism. In treating the patients he used thyroid extract and extracts prepared from the thymus and the suprarenal glands. Oppenheim (3) and Hoppe (4) reported improvement in patients following the administration of desiccated ovary and corpus luteum. It is evident, then, that many of the endocrine glands have been used in an attempt to link them as therapeutic adjuncts in the treatment of patients with hyperthyroidism.

Shapiro and Marine (5), in 1921, reported a case of exophthalmic goiter treated with whole ox suprarenal gland and with desiccated cortical tissue.

Reviewing the clinical course of the patient one notes that there was a control period of only ten days before the administration of the suprarenal gland preparations was begun. Within that period of time there were no definite evidences of

improvement. During the next forty days both fresh and desiccated ox suprarenal gland preparations were given by mouth without noticeable change in the clinical condition. Evidences of improvement such as gain in weight (12.3 kilos), lowering of the pulse rate and subsidence of the fever were noted after the patient had been given 15 grams a day of fresh whole suprarenal gland for a period of ten days. It is to be noted, however, that by that time the patient had spent fifty days in the hospital, a period of time during which one might expect improvement from the usual supportive measures not related to any specific therapeutic procedure. It is to be recalled that the superior thyroid arteries had been ligated eighty days previously. The suprarenal gland was discontinued for twenty-two days but during this time the patient continued to gain weight (7.3 kilos) and to show improvement in her general condition. During the next twelve days the gland therapy was administered, and there was a loss of 2.2 kilos in body-weight. She gained weight slowly after that and was discharged 131 days after admission. It is stated that at the time of her dismissal from the hospital she was clinically improved and had gained 19 kilos in weight.

The authors were of the opinion that the patient had improved while taking the cortical portion of the gland rather than during the administration of the dessicated whole gland. They also believed that this supplied added evidence "of a possible relative functional insufficiency of the suprarenal cortex as one of the underlying factors in exophthalmic goiter."

A few years later Shapiro (6) studied the effect of feeding interrenal gland in twenty cases of Graves' disease four of which he described in detail. These four patients were girls of the ages of 16, 19, and 19 years and a housewife 38 years of age. The preparation employed was a 50-per-cent glycerol emulsion of the cortex of fresh ox suprarenal glands. The average dose was 30 cc. per day by mouth. Of these four patients the girl of 16 years manifested clinical improvement and, after twenty-six days of bed rest and administration of the emulsion as described, the basal metabolic rate had decreased from +24 to −2 per cent. The patient's weight had increased 2.1 kilos. This girl was apparently well five months later. The three other patients gained weight but no real improvement was noted until after the thyroid gland had been irradiated. It seems desirable to be cautious in drawing conclusions from observations on a female patient of 16 years.

Shapiro states that he observed in the series of twenty cases beneficial results following the oral administration of the glycerol extract emulsion, chiefly in the increase in the body-weight and in the improvement of the muscle strength. He noted a rise in the blood pressure in patients who had a hypotension. There was an amelioration of dysmenorrhoea and marked improvement in diarrhea.

The cases are reviewed in some detail to emphasize the long duration of the observations made on patients who have a disease subject to

spontaneous remissions and which often responds so favorably to the non-specific measures such as rest in bed, sedatives, and high calorie diets.

Since the reports described (5, 6) indicated a possible beneficial therapeutic effect from the oral administration of suprarenal cortical tissue, it seemed desirable to re-investigate this phase of metabolism. In addition, the recent successful isolation (1) of a hormone of the suprarenal cortex facilitates the parenteral injection of proportionally huge amounts of the suprarenal cortical material.

The cortical tissue employed was prepared as follows:

The fresh beef suprarenals were separated from the peri-suprarenal fat, sliced sagittally, and the medullary portion carefully removed. The cortical tissue was ground finely, the material placed under oil to delay oxidation and kept on ice until used. Fresh material was prepared every twenty-four hours. It was removed from its protective layer of oil, warmed, and served as a raw meat sandwich. The patients ate the material without complaint and there were no gastro-intestinal symptoms following its ingestion. The stools were well formed and gave no evidence of lack of assimilation of the cortical tissue.

The cortical hormone employed was prepared by the method of Swingle and Pfiffner (7). Some of the hormone was furnished by these investigators from the laboratory at Princeton and the remainder was prepared in our own laboratory.

Since the hormone which was employed at the beginning of this investigation in October of 1930 was untried, it was first used upon the experimental animal. The data (8) obtained indicated that there were no deleterious effects, immediate or delayed, following the intravenous administration of a single large amount of the material (100 cc.) or repeated daily injections of 5 cc. for a period of thirty days. The material then was administered cautiously to man. The amounts employed were first small fractions of 1 cc. and later increased in amount until as much as a single injection of 40 cc. was given intravenously. No untoward results followed. In addition, following the administration of the hormone, there were no changes invoked in the oxygen consumption or in the respiratory quotient in either normal dogs or man.

The metabolism studies were performed chiefly by ourselves and in part by a trained technician. Samples of expired air for respiratory quotient and oxygen consumption determinations were collected in the usual manner and analyzed by the method of Haldane. In other experiments the basal metabolic rate was determined by use of the Krogh or Roth-Benedict type of spirometer.

The following observations were then made:

I. The effect of single and repeated injections intravenously of large amounts of the cortical hormone into individuals normal in respect to thyroid function.

II. The effect of repeated injections subcutaneously and intravenously of small amounts of the cortical hormone into patients with hyperthyroidism.

III. The effect of single and repeated injections intravenously of large amounts of the cortical hormone into patients with hyperthyroidism.

IV. The effect of repeated injections subcutaneously of small amounts of the hormone into patients with hypothyroidism.

V. The effect of feeding large amounts of raw suprarenal cortical material to patients with hyperthyroidism.

In group I five patients were investigated. Two of them had various minor complaints and low basal metabolic rates of −20 per cent.

TABLE I

Showing the number of patients in each age group treated by the parenteral administration of Cortical Hormone (Swingle-Pfiffner) and the average basal metabolic rate at the beginning and at the end of the treatment

	AGE			
	14–20 years	21–30 years	31–40 years	41–50 years
Number of patients	2	3	7	5
Average basal metabolic rate:				
Before treatment	+36	+55	+38	+39
After treatment	+42	+43	+37	+42

There was no other evidence, however, of hypothyroidism. It was found that neither isolated nor repeated injections of large amounts of the cortical hormone produced any appreciable change in the respiratory metabolism, pulse rate, temperature, general health, or subjective sensations of the patients.

In groups II and III a total of 17 patients were treated. There were 12 females and 5 males. The diagnosis in 14 was diffuse goiter with hyperthyroidism, in 3 nodular goiter with hyperthyroidism. The ages are as indicated in table I.

The amounts of extract administered either intravenously or subcutaneously varied from a single injection of 45 cc. to a total of 172 cc. given over a period of 25 days. The average amount for the group was 9.5 cc. per day. This was the amount of extract obtained from

285 grams of suprarenal cortex. No beneficial results were obtained by this method of treatment. Table II gives an example of a typical experiment.

Figure 1 summarizes the hospital course of one patient included in this group. The therapeutic approach was most difficult, as can be

TABLE II

Case 1. E. R., Unit No. 35701. Colored female, 34 years old

DATE	BASAL METABOLIC RATE	DAILY PULSE RANGE	WEIGHT	MEDICATION AND REMARKS
			kgm.	
2/24/31	+58	100–120	50.4	Admitted 2/21/31
3/ 6/31	+61	110–122	51.0	
3/10/31	+64	112–120	52.1	Suprarenal cortical hormone (Swingle-Pfiffner) 3 cc. intravenously twice daily
3/14/31	+63	108–124	53.6	
3/19/31	+68	108–122		
3/26/31	+66	116–122	54.2	
3/31/31	+74	100–118	54.7	
4/ 2/31	+62	106–116		
4/ 8/31	+61	112–120		
4/11/31	+70	116–128	55.7	
4/14/31	+67	110–132		Suprarenal cortical hormone discontinued 4/13/31
4/24/31	+63	114–120	56.7	Lugol's solution 3 cc. per day orally
5/ 7/31	+30	92–100	59.0	Subtotal thyroidectomy 5/9/31. Lugol's solution discontinued 5/14/31
5/28/31	+12	84– 92	59.0	Discharged
7/14/31	+6	80	59.1	Returned for examination

clearly judged. Suprarenal cortical extract was administered on the 188th day of her hospitalization; 10 cc. were given intravenously each day for a period of 17 days then 6 cc. a day for 13 days. At the end of this 25-day period of treatment the basal metabolism rate had decreased from +70 to +39. The ultimate course of the patient is shown. It seemed unjustifiable to ascribe the lowering of the metabolic rate to the influence of cortical extract since the material was used so late during the hospital stay, 188th day, and since radium treatment of the thyroid gland had been recently given and had already

resulted in a marked clinical improvement and a rise in the body-weight.

In group IV two patients were treated. One of these patients (table III) received 2 cc. of the material daily over a period of twelve days and then 3 cc. a day for a period of eleven days. The other, a white woman 48 years of age, a classical example of myxedema, was given

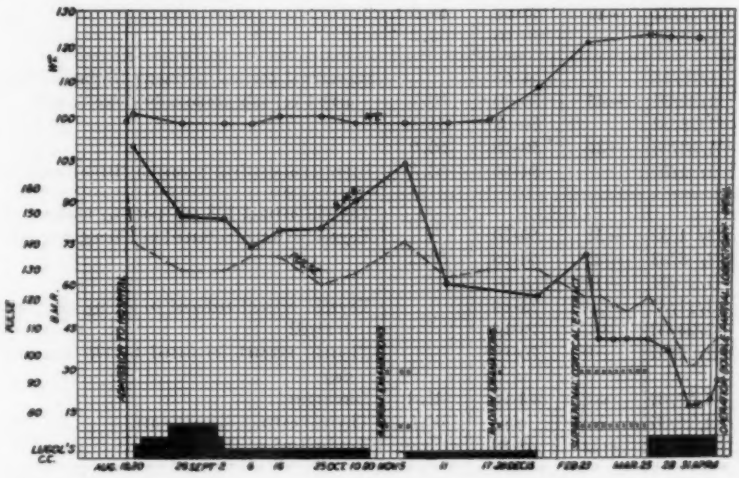

FIG. 1. G. L. B., WHITE FEMALE, 21 YEARS OF AGE. UNIT NO. 32, 711

A severe case of exophthalmic goiter, showing the initial failure to respond to Lugol's solution, the apparent beneficial results which followed radium emanations, the questionable response to suprarenal cortical hormone, and the final favorable response to Lugol's solution. Cortical extract administered on the 188th day of hospitalization. Total duration of hospital stay, 263 days.

6 cc. a day for a period of seventeen days. There were no changes discernible either in the oxygen consumption or the general condition of these two patients. Both of them made satisfactory clinical responses while taking thyroid extract.

In group V three patients were studied. Two were fed 12 grams of the prepared gland each day for a period of forty days. One of them was a colored male 33 years of age and the other a white male of 35

TABLE III

Case 11. D. B., Unit No. 41000. White female, 56 years of age

DATE	BASAL METABOLIC RATE	DAILY PULSE RANGE	WEIGHT	MEDICATION AND REMARKS
			kgm.	
1/ 6/32	−50	52–76	49.2	Admitted 1/4/32
1/ 9/32	−39	52–64		
1/14/32	−40	60–64	49.9	
1/18/32		58–66	50.2	
1/20/32		54–66		Suprarenal cortical hormone (Swingle-Pfiffner) 1 cc. subcutaneously twice daily
1/23/32	−45	56–60	50.7	
1/25/32		54–68	51.2	
1/30/32	−36	50–78	50.9	
2/ 1/32		54–64	50.3	Suprarenal cortical hormone discontinued
				Thyroid extract 128 mg. per day orally
2/ 4/32	−31	64–70		Thyroid extract increased to 196 mg. per day
2/ 6/32	−22	64–76	50.2	
2/10/32	−13	68–80		
2/17/32	−14	78–88		Thyroid extract reduced to 96 mg. per day 2/15/32
2/24/32	+2	76–84		
3/ 1/32	−9	76–80		Thyroid extract increased to 128 mg. per day
3/12/32	+4	84–88	47.4	Discharged
4/16/32	+5	68	49.0	Thyroid extract discontinued
5/11/32	−22	68–84	50.0	Readmitted 4/30/32
5/16/32	−26	72–80	51.0	*Suprarenal cortical hormone (Swingle-Pfiffner) 1.5 cc. subcutaneously twice daily
5/20/32	−26	62–72	52.0	
5/23/32	−26	64–72	52.1	
5/27/32		64–72	52.8	*Suprarenal cortical cortical hormone discontinued
5/28/32				Discharged. Thyroid extract 128 mg. per day orally started
6/11/32	−16	67	52.7	Returned for examination
7/23/32	−5	78	52.7	Returned for examination
11/26/32	+7	85	53.7	Returned for examination

* Concentrated extract prepared from whole glands according to new technique of Swingle and Pfiffner.

years (table IV). In each instance a preliminary control period of thirty days was employed before the feeding experiment was begun. Beneficial results which could be attributed directly to the therapy

used were not noted. Both patients showed a typical beneficial response following the administration of Lugol's solution, were successfully operated on, and have remained well. A third patient, a white

TABLE IV

Case 9. W. S., Unit No. 40464. White, male, 35 years of age

DATE	BASAL METABOLIC RATE	DAILY PULSE RANGE	WEIGHT	MEDICATION AND REMARKS
			kgm.	
12/ 2/31	+55	112–120	67.3	Admitted 12/1/31
12/ 8/31	+46	88–116	67.3	
12/14/31	+62	96–104	65.4	
12/21/31	+53	94–104	65.9	
12/28/31	+45	100–112	65.9	
12/30/31		92–108	66.0	Whole raw beef suprarenal glands 5 grams
1/ 2/32	+36*	92–112	65.6	per day orally
1/ 5/32	+33*	90–104	64.9	Raw suprarenal glands increased to 7.5 grams per day 1/4/32
1/ 8/32		90– 98	64.0	Raw suprarenal glands increased to 10 grams
1/11/32	+60	84–102	64.0	per day
1/13/32	+50	92–110		
1/18/32	+48	88–108	63.6	
1/21/32	+50	90– 98		Raw suprarenal glands increased to 15 grams
1/25/32	+53	94–106	64.1	per day
1/28/32	+70	88–120	64.8	
2/ 2/32	+43	90–110	65.0	Raw suprarenal glands increased to 20 grams
2/ 5/32	+42*	88–108	64.4	per day 2/1/32
2/ 8/32	+47	96–104	67.7	Raw suprarenal glands discontinued
2/11/32	+42	90–108		Lugol's solution 3 cc. per day orally started
2/19/32	+29	78–100	68.4	2/9/32
2/23/32	+18	78– 94	69.8	Subtotal thyroidectomy 2/24/32. Lugol's solution discontinued 2/28/32
3/11/32	+8*	84– 94	70.3	Discharged 3/12/32
6/25/32	+5	68	75.7	Returned for examination
9/ 3/32	−1	64	83.0	Returned for examination

* Tests only fairly satisfactory.

girl of 17 years, was given 35 grams of the prepared cortex each day for a period of 30 days without any striking beneficial results.

Table V gives a summary of the patients treated and indicates the average daily amount of the cortical hormone administered. It is

certainly obvious that the amount of raw suprarenal cortex administered in the form of suprarenal cortical extract, 120 to 285 grams, is in marked excess of any amounts administered to the patients reported by the authors quoted. Indeed, it is ten to fifteen times the amount

TABLE V

Patients treated intravenously and subcutaneously with suprarenal cortical hormone

Duration of treatment, total amount of extract given, and amount of extract a day expressed in cubic centimeters and in the weight of suprarenal cortex required in its preparation, are indicated.

NUMBER OF PATIENTS	DIAGNOSIS	TOTAL AMOUNT OF SUPRARENAL EXTRACT	DAYS UNDER TREATMENT	AMOUNT OF EXTRACT PER DAY	
				In cubic centimeter	In grams of cortex
		cc.			
5	Normal controls	(10–72) average 40	(1–11) average 4.8	8.3	249
17	Hyperthyroidism	(10–242) average 88	(1–30) average 12.5	9.5	385
2	Hypothyroidism	(57–102) average 79.5	(17–23) average 20	4.0	120

TABLE VI

Patients fed fresh hashed suprarenal cortex

The amount of suprarenal cortical tissue administered is expressed as a total and as the average of grams a day.

NUMBER OF PATIENTS	DIAGNOSIS	TOTAL AMOUNT OF CORTICAL TISSUE	DAYS OBSERVED	AMOUNT OF CORTICAL TISSUE GIVEN PER DAY
		grams		*grams*
3	Exophthalmic goiter	(480–1050) average 670	(30–40) average 36	18.6

of cortical tissue which we were able to administer orally to our patients, as indicated in table VI. Here the amount of raw cortical tissue fed to the patients (18.6 grams a day) is quite comparable to the amounts given the patients in whom beneficial results were reported (5, 6).

Marine and Baumann (9, 10, 11, 12) reported experiments to show that partial destruction of the suprarenal cortex in rabbits with intact thyroids resulted in an increase in heat production. They were unable to obtain these results if the thyroid gland had been removed prior to the operation of partial ablation of the suprarenals. Later they (13) fed a glycerol emulsion of ox suprarenal cortex to rabbits and reported a decrease in the oxygen consumption of these animals. It is of interest that positive results were obtained in only 11 of the 18 rabbits which they followed. From these data the authors concluded that the suprarenal gland normally elaborates a hormone which exercises an inhibitory or regulatory influence over the secretory activity of the cells of the thyroid gland.

Work from this laboratory on a large series of suprarenalectomized dogs during the past two years has shown no evidence of any increase in oxygen consumption as a result of this procedure.

Recently it has been demonstrated (14) that plant juices contain a reducing substance that is capable of preventing hyperplasia of the thyroid gland in rabbits. The thought is advanced that the suprarenals and gonads serve as a possible source of, and certainly a storehouse for, this reducing substance which normally prevents or corrects hyperplasia of the thyroid by providing another mechanism for promoting tissue oxidation. The authors were inclined to identify this substance as hexuronic acid (15).

It is to be remembered that there are patients with Addison's Disease in whom the pathological change in the suprarenal glands is a selective atrophy of the cortical portion (16, 17, 18). In some of the cases reported it is estimated that practically all (98 to 99 per cent) of the total cortical tissue had been destroyed, and certainly in all of the cases there was not sufficient cortical tissue to maintain life. If it is assumed that the suprarenal cortex prevents hyperplasia of the cells of the thyroid gland, one would indeed expect to find marked hyperplasia of the thyroid cells in these cases and an elevation of the basal metabolic rate. On the contrary, the thyroid in these instances is never enlarged and usually there is a marked atrophy of the gland tissue. In addition, these patients have low basal metabolic rates.

The work of recent years seems to indicate that the pituitary gland merits consideration when one attempts to evaluate the relationship

of the thyroid and suprarenal glands. Smith (19) has shown that following hypophysectomy in the rat an atrophy of the suprarenal cortex and an involution of the thyroid occur. By means of "anterior homeotransplants" these glands could be returned to a normal histological condition. If there was a primary interrelationship between the thyroid and suprarenals, one would anticipate a hyperplasia of the thyroid to be associated with the atrophy of the suprarenal cortex. This condition has not been recorded.

Moreover, a hormone elaborated by the anterior lobe of the hypophysis which stimulates the thyroid has been recently demonstrated. This hormone does not effect metamorphosis of the salamander after removal of the thyroid, which seems to indicate that the hormone had a direct action on the cells of the thyroid. The authors (20) believe it to be a specific stimulator of the thyroid, though it cannot replace the thyroid hormone. Similar results (21, 22) have been obtained in the guinea-pig. In addition, in the duck exophthalmos has been produced (23).

SUMMARY

From the experimental work reviewed one might infer that a beneficial result would follow the administration of raw suprarenal cortex by mouth or the parenteral administration of the suprarenal cortical hormone to patients with hyperthyroidism. With neither method of therapy were we able to obtain any definite improvement in the general nutrition of the patients or any diminution in the signs of the disease which were present. Nor were we able to note any changes following the administration of the cortical hormone to normal patients or patients with hypothyroidism.

It might be suggested that the method employed in the extraction of the cortical tissue produces an extract which contains a hormone capable of maintaining life in bilaterally suprarenalectomized animals, but not the hormone postulated to regulate thyroid function. It is known (24) that in suprarenalectomized dogs kept in a state of good nutrition for periods of time as long as one year by use of the suprarenal hormone (Swingle-Pfiffner) the thyroid gland does not show hyperplastic changes. On the contrary, atrophy of the thyroid is usually seen. If the extract employed contained only the hormone which

maintains life and not the substance which exerts the regulatory action on the thyroid, one would certainly expect to find hyperplasia in the thyroid cells.

This fact supplies added evidence that the extract employed should have produced retardation of the overactivity of the thyroid in the patients, if the theory advanced by Marine and his associates is tenable.

CONCLUSIONS

1. Five normal patients, 17 patients with hyperthyroidism, and 2 patients with hypothyroidism were treated with suprarenal cortical extract (Swingle-Pfiffner). No clinical improvement was noted.
2. Three patients with hyperthyroidism were fed raw suprarenal cortical tissue. In no case did beneficial results follow.
3. Certain theories of thyroid-suprarenal relationship are discussed.

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